Liste des abréviations

AFSSAPS	Agence Française de Sécurité SAnitaire des Produits de Santé
AKIN	Acute Kidney Injury Network
AMM	Autorisation de Mise sur le Marché
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
CAPTV	Centre AntiPoison et de ToxicoVigilance
CCTV	Comité de Coordination de la toxicovigilance
CHU	Centre Hospitalo-Universitaire
CSF	Cerebrospinal fluid
CVVH	Continuous VenoVenous Hemofiltration
EEG	Electroencephalogram (électroencéphalogramme)
EKG	Electrocardiogram (électrocardiogramme)
ESBRA	European Society for Biomedical on Alcoholism
GABA	Gamma-Aminobutyric Acid (acide gamma-aminobutyrique)
GCS	Glasgow Coma Scale
ICU	Intensive Care Unit
IQR	Interquartile
ISBRA	International Soxiety for Biomedical Research on Alcoholism
LCR	Liquide céphalo-rachidien
MESH	Medical Subject Heading
MDRD	Modification of Diet in Renal Disease
NMDA	N-méthyl-D-aspartic acid (Acide N-méthyl-d-aspartique)
PCC	Poison Control Center
RRT	Renal Replacement Therapy
RTU	Recommandation temporaire d'utilisation
SAPSII	Simplified Acute Physiology Score II

PLAN

Baclofen self-poisoning in the era of changing indication: a retrospective multicentric study from a poison center.

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Baclofen self-poisoning: is extrarenal epuration efficient in patient without kidney dysfunction?

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Répartition du travail

LEGER Maxime :

Revue de la littérature/bibliographie, recueil de données, focalisation sur le retentissement clinico-biologique des intoxications et sur les ressources engagées. Réalisation de la partie statistique concernant cet axe, avec utilisation du site http://marne.u707.jussieu.fr/biostatgv/, et mise en page des tableaux.

Ecriture et finalisation du projet en vue de la soumission d'un article concernant l'aspect épidémiologique des intoxications au baclofène, et la morbi-mortalité associé.

Présentation e-poster prévue en janvier 2016 pour le congrès SRLF.

BRUNET Marion :

Revue de la littérature/bibliographie, recueil de données. Travail sur l'aspect pharmacocinétique et sur l'utilité de l'hémodialyse dans la prise en charge des intoxications au baclofène. Ecriture et finalisation du projet en vue de la soumission d'un article.

INTRODUCTION

Le baclofène est une molécule synthétisée depuis 1962 et utilisée initialement comme traitement anti-spastique de la sclérose en plaques, des affections médullaires ou d'affections d'origine centrale [1]. L'autorisation de mise sur le marché (AMM) est obtenue en France en 1974. Cette molécule est utilisée dans cette indication, par voie intrathécale ou orale, à des doses allant communément de 30 à 120 mg par jour.

A partir des années 1990, cette molécule a été étudiée dans le champ des addictions, principalement à la cocaïne [2], et dans celui du sevrage alcoolique, sur le modèle animal [3]. Son efficacité semble surtout intervenir contre le phénomène de « craving », l'envie irrésistible de boire, qui est une cause fréquente de rechute et d'échec de l'abstinence [4].
En 2005, le Dr Ameisen, un cardiologue français exerçant à New York et souffrant d'addiction à l'alcool, publie un article sur sa propre expérience d'automédication par le baclofène à des doses *per os* allant de 30 mg jusqu'à 270 mg pour une disparition du phénomène de craving pendant 9 mois [5]. Il fait ensuite connaître le baclofène auprès d'un large public en 2008 avec la publication de son ouvrage autobiographique *le dernier verre* [6]. Les patients réclament auprès de leur médecin ce remède, nouvellement médiatisé dans cette indication. L'utilisation du baclofène suscite nombreuses interrogations, débats et polémiques au sein de la communauté médicale. Concernant son efficacité, plusieurs essais montrent des résultats contradictoires : Addolorato en 2007 montre une abstinence pour 71% des patients sous baclofène contre 29% pour le groupe placebo (n=84) [7] alors qu'en 2010, Garbutt ne montre pas de de différence significative de la durée d'abstinence entre les 2 groupes baclofène/placebo [8]. Une revue Cochrane récente a tenté d'évaluer l'efficacité de l'utilisation du baclofène dans le cadre des syndromes de sevrage éthylique. Elle a compilé les résultats de l'ensemble des études cliniques randomisées contrôlées évaluant l'efficacité

du baclofène comparé à un autre traitement médicamenteux ou à un placebo. Celle-ci conclue à un manque de preuves pour recommander l'utilisation du baclofène dans le contexte d'aide au sevrage éthylique [9]. Il n'a été publié et retenu, dans cette revue, que deux études (recueil jusqu'en janvier 2015), regroupant 81 participants [10,11]. La place du baclofène comme traitement pour réduire la consommation quotidienne d'alcool reste finalement toujours controversée.

L'agence française de sécurité sanitaire des produits de santé (AFSSAPS) autorise en 2012 les essais cliniques contrôlés « Bacloville » en ville puis « Alpadir » en milieu hospitalier. Les résultats ont été présentés lors du congrès international ISBRA-ESBRA à Berlin le 03 septembre 2016. Incluant 158 patients sous baclofène (posologie quotidienne maximale de 180 mg/j) et 162 patients sous placebo, l'étude Alpadir met en valeur une diminution de la consommation journalière d'alcool de 9,5 à 4 verres pour les patients sous baclofène contre 5 verres pour ceux sous placebo, sans significativité. De même, il n'y aurait pas de différence significative pour le maintien de l'abstinence (11,9% vs 10,5%) [12]. L'étude la plus attendue, Bacloville, montre des résultats encourageants avec 56,8% des patients sous baclofène (posologie quotidienne maximale de 300 mg/j) devenus abstinents ou ayant une consommation à faible risque, contre 36,5% pour les patients sous placebo. Les résultats concernant la tolérance n'ont à ce jour pas été communiqués [13]. Un essai sur environ 800 patients volontaires a été lancé début 2016 par le CHU de Lille pour étudier les effets secondaires du baclofène.

En mars 2014, l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) finit par mettre en place une recommandation temporaire d'utilisation (RTU) pour encadrer la demande croissante de prescription de baclofène. Les posologies peuvent dans ce cas aller jusqu'à 300 mg par jour, mais les prescriptions sont soumises à la consultation

régulière d'un médecin addictologue, voire d'un psychiatre [14]. En juillet 2015, on dénombrait environ 6000 patients inclus dans la RTU.

Le baclofène devrait bénéficier d'une extension de son AMM ; le laboratoire Ethypharm vise la commercialisation de sa spécialité au cours de l'année 2017.

Le baclofène est un analogue structural du GABA (acide gamma amino-butirique), qui ralentit la transmission des réflexes mono- et polysynaptiques par stimulation des récepteurs GABA(B) de la moelle épinière [15].

L'activation des récepteurs GABA(B) induirait une inhibition des neurones dopaminergiques réduisant ainsi la libération alcoolo-induite, dans le striatum, de dopamine, neurotransmetteur de l'apprentissage plus que du plaisir [16]. D'autre part, l'activation par la voie GABA-médiée contrebalancerait la fonction excitatrice de la voie glutamate/NMDA-médiée, exacerbée dans les syndromes de sevrage [17].

Du fait de son mécanisme d'action, le baclofène est un puissant dépresseur du système nerveux central responsable d'effets indésirables et pour lequel une tolérance s'installe rapidement. Une augmentation progressive des doses permet de limiter les effets secondaires centraux [18].

En 1976, un premier cas d'intoxication avec 900 mg de baclofène, nécessitant plus de 72 heures de soins intensifs, est publié [19]. Depuis, le profil toxicologique du baclofène a été décrit et étayé [20]. On retrouve initialement une agitation, des hallucinations, délires, une désorientation temporo-spatiale. Survient ensuite une dépression du système nerveux central allant jusqu'au coma, caractérisé par un tracé de « *burst* suppression » à l'électroencéphalogramme [21]. Cette dépression centrale est associée à une dépression respiratoire, une hypotonie, une hyporéflexie, des myoclonies, des convulsions. Sur le plan

cardiovasculaire, on peut observer une hypo- ou une hypertension, une bradycardie ou une tachycardie sinusale, des troubles du rythme et des troubles jonctionnels pouvant conduire à un arrêt cardiaque. Coma, délire et convulsions seraient surtout observés pour des doses supérieures à 200 mg [22].

Le baclofène est rapidement et complètement absorbé dans le tractus digestif. Lors d'une administration orale de doses uniques de 10 à 30 mg de baclofène, les pics plasmatiques sont observés au bout de 30 min à 1h30. La concentration plasmatique thérapeutique se situe entre 0,08 et 0,4 mg/L. Dans le liquide céphalo-rachidien, la substance active atteint des concentrations qui demeurent 8,5 fois plus faibles que dans le plasma. La demi-vie plasmatique du baclofène est estimée entre 3,5 h et 6,8 h [23]. Le baclofène a un faible volume de distribution (Vd), égal à 0,7 L/kg, un faible taux de liaison aux protéines sériques (environ 30 %) et une élimination essentiellement rénale (à 75% sous forme inchangée) [24]. Ses propriétés pharmacologiques et physicochimiques (molécule hydrosoluble, modérément lipophile et de petit poids moléculaire : 213,7 g/mol) en font une molécule dialysable.

La prise en charge est symptomatique et réanimatoire dans les cas les plus sévères. Pour limiter l'absorption du toxique, le charbon activé est indiqué en cas de prise en charge précoce sans troubles de conscience. Chez les patients insuffisants rénaux, l'hémodialyse peut être proposée en cas de tableau sévère d'intoxication. En effet, on observe des demi-vies d'élimination plus longues que chez les patients avec une fonction rénale normale alors que les concentrations maximales ne sont pas significativement différentes [25]. Les intoxications seraient potentiellement plus longues et sévères. Plusieurs cas rapportés ont montré des réductions des demi-vies d'élimination (12,6 h à 3,7 h [26] ou encore 15,5 h à 2,06 h [27]) associées à une amélioration rapide de la présentation clinique. Le recours à

une hémofiltration veino-veineuse continue dans ce type d'intoxication, chez des patients avec des fonctions rénales préservées a été rapportée dans quelques cas cliniques, sans démontrer de supériorité par rapport à l'hémodialyse, ni de bénéfice clinique [28-30]. La prise en charge par la réalisation d'une épuration extra-rénale chez les patients avec une fonction rénale conservée reste controversée [31].

En 2012, l'ANSM a sollicité le Comité de coordination de toxicovigilance (CCTV) afin de mesurer l'impact de la sortie du livre *Le dernier verre* sur les cas notifiés aux centres antipoison (CAPTV).

Cette étude a montré, particulièrement entre 2009 et 2010, une augmentation du volume des ventes de baclofène, du nombre de patients traités par baclofène et des cas notifiés aux CAPTV (même après ajustement sur les ventes et nombre de patients) [32]. Ces résultats suggèrent un impact particulier du baclofène sur cette population. Le baclofène est devenu plus accessible à une population de patients en sevrage alcoolique, plus volontiers à risque de dépression et de passage à l'acte suicidaire. Roy rapporte qu'environ 40% des patients alcooliques chroniques suivis dans sa cohorte ont effectué une tentative de suicide au cours de leur vie [33]. Ces patients sont plus enclins à présenter des pathologies psychiatriques, majorant le risque d'intoxication médicamenteuse volontaire et de plus mauvais pronostic [34].

Le but de cette étude est dans un premier temps de décrire l'épidémiologie, la morbidité et la mortalité du baclofène dans ce contexte récent d'utilisation croissante, à des doses plus importantes que dans l'indication habituelle.

Dans un second temps, la place de l'hémodialyse, controversée sera discutée dans la prise en charge de ce type d'intoxication.

Ces deux axes de recherche ont été rédigés sous le format de deux articles, dans l'objectif de publier les résultats de ce travail.

ARTICLE 1

Baclofen self-poisoning in the era of changing indication: a retrospective multicentric study from a poison center.

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1. Abstract

Background: The lack of an effective treatment for the maintenance of abstinence from alcohol has led physicians to take in interest in baclofen. Beyond efficacy, safety of baclofen, prescribed in high doses, is a concern, especially in case of drug overdose. Indeed, patients with chronic alcohol abuse frequently develop psychiatric disorders, and are at risk of voluntary drug intoxications. Thus, we set up a retrospective study to describe morbidity and mortality associated with baclofen overdose.

Material and Methods: A case was defined as exposure to baclofen in self-harm attempt with or without symptoms between January 2008 and December 2015. This study was based on data collected by the Poison Control Center (PCC) of Angers University Hospital during telephone responses to toxicological exposure and during patient follow-up, supplemented by reports from clinical staff in hospital. The mortality rate of baclofen poisoning cases was compared to the 31859 non-baclofen voluntary drug poisoning cases declared to the PCC of Angers University Hospital over the same period.

Results: 190 cases (median age: 40 years; gender (female): 46.8%) of voluntary intoxications were reported, including two deaths diagnosed at first medical assessment.

Over years, number of baclofen poisoning grew up from 8 cases in 2008 to 91 cases in 2015. 111 patients (59%) had GCS ≤ 12 at admission and 77 had GCS > 12 (41%). Eighty patients required mechanical ventilation (42.6%). Neurological severity (GCS ≤ 12 or > 12) was significantly associated with higher suspected ingested dose (400 [IQR=190-685 mg] vs 120 [IQR=80-300 mg], p<0.0001) and higher baclofen blood concentration (3.24 mg/l [min-max=0.05-14.82 mg/l] vs. 0.32 mg/l [min-max=0-1.66 mg/l], p < 0.001). Seizures were frequently observed in patients with GCS <12 (n=24, 22% vs. n=2, 3%, in patients with GCS> 12, p < 0.001). Three patients died in the hospital (hospital mortality rate 1.6%, total mortality rate 2.6%). Non-baclofen cases had lower rate of endotracheal intubation (n=1833, 6%, p < 0.001 for comparison) and mortality rate (n=299, 0.1%, p=0.02 for comparison).

Conclusion: Baclofen, prescribed in high doses, may lead to severe intoxications: self-poisonings frequently require endotracheal intubation and are associated with an increased risk of death. Dialysis decreases baclofen elimination half-time but clinical relevance of this difference could not be determined.

2. Introduction

Baclofen, a derivative of γ-aminobutyric acid, is a selective agonist of the receptor GABA(B) which activation may reduce dopamine release and N-methyl-D-aspartate transmission [35]. It has been originally indicated to treat central spasticity [1], but has recently been considered to treat chronic alcohol abuse. Although efficacy of baclofen therapy in this last indication is still debated pending publication of several trials, its use has spread tremendously over years in France [6-8]. In 2012, number of patients treated for alcohol was estimated at 100,000.

Patients suffering from chronic alcohol abuse have an increased frequency of mood disorders and are at high risk of suicide attempt, in particular drug overdose [36,37]. Thus, evaluation of the benefit/risk balance of a new treatment in this population requires special attention to acute toxicity in self-poisoning. Furthermore, baclofen as treatment for alcohol abuse is often prescribed in doses higher than for its classical spasticity indication, which makes possible massive drug overdose as a consequence of easier drug availability.

Baclofen acute toxicity has been reported in small series of patients suffering of spasticity, showing neurological toxicity [17,38,39]. The aim of this study was to describe the epidemiology, morbidity and mortality of baclofen in the context of its widespread use for alcohol abuse.

3. Materials & methods

This retrospective observational study was based on the phone declarations from all emergency departments and intensive care units of Western France, representing a population of more than 12 million people and 50 university and general hospitals, to the Poison Control Center (PCC) of the Angers University Hospital, Angers, France. All suspected cases of baclofen self-poisoning, either in isolation or in combination with other toxicants, or from January 2008 to December 2015 were included. The Angers University Hospital ethics committee approved this study and waived the need for patient consent (approval number: 2015-89).

1. Data analyzed

The following data were collected from PCC files and from medical reports of the hospitals in which patients had been admitted for the self-poisoning: *demographic data:* age, gender, weight, past medical history of chronic alcohol abuse (as noted in medical files) and psychiatric diseases (follow-up by a psychiatrist or antidepressant or neuroleptic drug in

usual treatment), indication for baclofen therapy (spasticity, alcohol abuse, treatment of a relative), previous suicide attempt(s); *self-poisoning characteristics:* baclofen suspected ingested dose (SID), drug(s) co-ingested, baclofen blood concentration(s), alcohol blood concentration; *self-poisoning acute manifestations and outcome:* Glasgow coma score (GCS) at hospital admission, presence of delirium requiring sedative agents, seizures, electrocardiographic abnormalities, acute kidney injury, electroencephalographic (EEG) abnormalities, aspiration pneumonitis; *organ support requirement and outcome:* mechanical ventilation, renal replacement therapy (RRT), vasopressor use, ICU and hospital length of stay, hospital mortality. In addition, SAPSII and SOFA scores were extracted from medical files in ICU patients [40,41]. The role of baclofen in the death of patients is evaluated by the French calculation method of imputability in toxicovigilance (v7.6). It is a five-step scale (null, not excluded, possible, probable, highly probable) based on clinical, paraclinical, circumstances and bibliometric criteria (using the present website: https://tv.toxalert.fr/v7.6/Calcul_imputabilite_v7.6.html).

2. Control group

Hospital mortality and requirement for mechanical ventilation in baclofen self-poisoning patients were compared with the 31,859 non-baclofen self-poisoning episodes reported to the Poison Control Centre (PCC) of Angers University Hospital, between 2008 and 2015.

3. Statistical analyses:

Baclofen self-poisoning patients were divided into two groups according to nadir GCS. Patients with GCS ≤12 constituted the severe intoxication group and patients with GCS >12 constituted the non-severe intoxication group. This threshold corresponds to the transition from minor to moderate symptoms of the nervous system in the poison severity score, a standardized scale for grading the severity of poisoning [42].

Data were presented as median (interquartile range or minimum and maximum values) or n (%) as appropriate. Between-group comparisons were performed using Chi2-test for categorical data, Mann-Whitney test for continuous data. The Pearson Product-Moment Correlation was used between-group comparisons for continuous data. A value of P<0,05 was considered statistically significant.

4. Results

Baclofen self-poisoning reported to PCC increased by an 11.3 factor from 2008 to 2015 due to a major increase of self-poisoning in patients taking baclofen for chronic alcohol abuse (see figure 1).

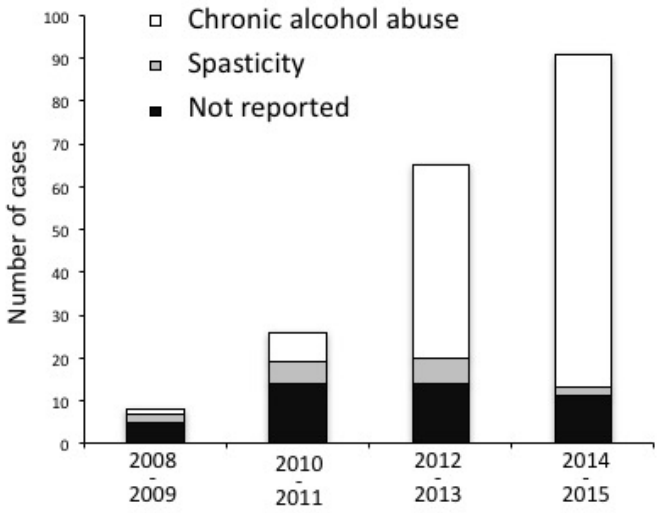

Figure 1: chronological distribution

One hundred and ninety episodes of self-poisoning in 190 patients were therefore included for analysis. Among these, 2 deaths were diagnosed at home at first medical evaluation by emergency services. Among the 188 remaining patients, 111 patients (59%) had GCS ≤ 12 at the first medical assessment, and 77 patients (41%) had GCS > 12. Descriptive results of the severe and non-severe groups are given in Table 1. Patients in the severe group had more frequent chronic alcohol abuse at the limit of significance. Although past history of psychiatric diseases was extremely frequent in both groups, severe patients suffered significantly more frequently of mood disorders.

Patients with severe self-poisoning had higher suspected ingested dose ($p<0.001$) and were frequently admitted to the ICU and ventilated. SAPSII score and SOFA score in ICU-admitted patients were 44.5 (36-58) and 5 (4-7) respectively. Severe patients had more frequently seizures than non-severe patients ($p<0.001$). Delirium requiring sedative agents was frequent but not significantly different between the two groups. EKG was rarely performed in non-severe patients; in severe patients 12 out of 96 (13%) patients with EKG performed showed mild QT prolongation (co-ingestion of other toxicant may have played a role in 6 patients). Of note EEG was performed in 25 ICU patients and showed burst suppression in 12. Baclofen blood concentration was rarely measured and was significantly higher in severe patients. Renal replacement therapy was performed in 12 ICU patients. Indication for RRT was acute kidney injury in 4 patients. On the opposite, in the remaining 8 patients RRT was started solely for the purpose of baclofen blood purification in the absence of any significant renal impairment.

In comparison to non-baclofen self-poisoning episodes declared to the PPC of Angers on the 2008-2015 period, baclofen self-poisoning was associated with a more frequent requirement for mechanical ventilation (1833/31,859 (5.7%) vs. 80/190 (42%) respectively, $p<0.001$) and a higher frequency of death (299/31859 (0.1%) vs. 5/190 (2.6%) respectively, $p=0.02$).

Of the 5 deceased, cause of death was related to a cardiac arrest at first medical evaluation for three cases, including one patient initially resuscitated but who eventually deceased of post-anoxic encephalopathy. One patient had post-convulsive encephalopathy conducting to a withdrawal of life-supporting techniques. One patient had an in-ICU late hypoxic cardiac arrest occurring in a context of critical illness polyneuromyopathy. Imputability of baclofen in these patients could be qualified as possible or highly probable for 3 and 2 patients, respectively.

Tableau I : Demographic data and self-poisoning characteristics of the 188 patients admitted alive to the hospital

	Severe Baclofen self-poisoning (GCS ≤ 12) n=111 (59 %)	Non-severe Baclofen self-poisoning (GCS > 12) n=77 (41 %)	p
Female	55 (49.5%)	34 (44.2%)	0.46
Age, years	41 [33-48]	39 [30-49]	0.25
Chronic Alcohol Abuse	93 (83.7%)	52 (67.5%)	0.05
Missing data	*5 (4.5%)*	*9 (11.7%)*	
Any psychiatric diagnoses	74 (67%)	46 (60%)	0.33
Missing data	*13 (12%)*	*11 (14%)*	
Mood disorders	63 (57%)	28 (36%)	<0.01
Baclofen indication			
Spasticity	8 (7.2%)	7 (9.1%)	
Chronic alcohol abuse	82 (73.9%)	49 (63.6%)	0.13
Treatment of a relative	4 (3.6%)	8 (10.4%)	
Missing data	7 (6.3%)	13 (16.8%)	
Combined drug intoxication,	71 (64 %)	48 (62.3%)	0.82
Suspected ingested dose, mg	400 (190-685)	120 (80-300)	<0.001
Patients with baclofen blood determination	30 (27%)	4 (5%)	<0.001
Baclofen blood concentration, mg/L*	3.24 [1.5-5.04]	0.32 [0.11-0.79]	<0.001
Glasgow coma score	6 [3-9]	15 [14-15]	<0.001
Delirium requiring sedative agents	29 (26%)	21 (27%)	0.94
Seizure	24 (22%)	2 (3%)	<0.001
Aspiration pneumonitis	33 (41%)	0	< 0.001
ICU admission	81 (73%)	0	< 0.001
Mechanical ventilation	80 (72%)	-	
Duration of mechanical ventilation, hours	48 [24-96]	-	
Vasopressor use	17 (21%)	-	
Renal replacement therapy	12 (11%)	-	
ICU length of stay, hours	96 [48-164]	-	
Hospital length of stay, hours	120 [48-164.25]	24 [12-30]	<0.001
Hospital mortality	3 (3%)	0	0.3

Data are n(%) or median [interquartile]
ICU : Intensive Care Unit
* First sampling

5. Discussion

This retrospective study collecting data from a poison center covering a large portion of the French territory and french population (20%) showed a more than 11-fold increase in the number of Baclofen self-poisoning episodes over recent years. This increase was related mainly to prescription for alcohol chronic abuse. Delirium and seizures were frequently observed. Baclofen self-poisoning was characterized by a high frequency of mechanical ventilation (80%) and death (2.6%), with more than a 7-fold and 26-fold increase respectively in comparison to non-baclofen poisoning.

A nearly tripling from 2007 to 2011 of sales of Baclofen has been reported in France. Thus, the increase in self-poisoning impressively exceeded what could be expected from this figure. Awareness of baclofen changing indications may have lead practitioners to report more frequently cases of self-poisoning but this is unlikely to solely explain the observed major increase. Of note, this increase is not universal, as the Danish nationwide register-based survey, showed no increase of baclofen intoxication despite increased sales [43]. Alcohol-dependent persons have an increased risk of panic and bipolar disorders [44] and have a high level of impulsivity [45]. All these conditions enhance the risk of suicide. In addition, it has been shown that high-dose baclofen intake can increase impulsivity, trigger aggressive behaviour and as consequence raise the suicidal risk through activation of the mesolimbic dopamine system [46,47]. During Finally, the association between mood disorders and increase acute severity of self-poisoning observed in this study has already been reported in the literature, evidencing a potential link between the intensity of the willing to die and toxicant ingested dose [48]. Taken all these data together, prescribing baclofen in patients with chronic alcohol abuse may induce deleterious interactions leading to frequent and

severe intoxications. However, this should be balanced with the potential reduction in mortality and morbidity due to alcohol abuse cessation if proven in pending studies.

Several reports already insisted on the frequency and severity of baclofen-induced encephalopathy with delirium, seizures, burst suppression on the EEG and leading to mechanical ventilation, aspiration pneumonitis and eventually death [43,49-52]. Rate of intubation and mechanical ventilation has been reported from 30 to 50% in these studies, which is a strong marker of the frequent severity intoxication. Our results, being the largest series to our knowledge, confirm and extend all these data in the era of baclofen prescription for chronic alcohol abuse [53]. Importantly, being poison center-based and not hospital-based, our study allowed to take into account deaths occurring at home. This was not the case in previous studies that reported a lower frequency of fatal outcome, missing a major aspect of the clinical picture [20,43,49,54].

Several characteristics discriminated significantly severe and non-severe cases. Seizures were mainly observed in the most severe cases with altered consciousness. Baclofen is a known proconvulsivant drug which increases neural excitation contrast in some parts of the brain [55]. On the opposite delirium was observed equally across severe and non-severe cases. One may wonder whether delirium is related to alcohol withdrawal or to baclofen, which cannot be determined on our dataset. One particular point of the more severe cases in the fact that the median suspected ingested dose (400mg) is modestly superior to the upper range of prescribed daily dose in some trial (300 mg) [10,16]. Such high doses, can be indeed well tolerated thanks to a titration phase of several weeks [16]. However, our study shows that the difference between therapeutic and toxic doses is very close and that the titration phase is of utmost importance. In this study, baclofen blood concentrations were

done more frequently in patient with severe self-poisoning (30%). Use of dialysis was relatively frequent, notably in patients without renal impairment. It reflects the debate on its usefulness in baclofen poisoning [56]. Our data did not permit to analyse the clinical impact of this technique.

Several biases limit the interpretation of our results. Declarations to poison centres are dependent on physician decision and may favour declaration of more severe cases. Co-ingestion of multiple drugs was frequent and it was impossible to discriminate the respective role of the different drugs ingested concomitantly. One major point is the lack of long-term follow-up. Indeed, it has been shown that patients after suicide attempt have prolonged excess of risk to die from various causes [48,57]. Unfortunately, it was impossible to obtain the exact number of patients treated for alcohol abuse with baclofen over the study period on the same region. This could have permitted to describe accurately the excess of risk of self-poisoning in this population. In the absence of such data, we only rely on extrapolations that should be taken with caution.

In conclusion, baclofen self-poisoning increased tremendously over the recent years due to increased prescription for alcohol abuse. Baclofen self-poisoning was characterized by encephalopathy with consciousness alteration, seizures and delirium frequently requiring mechanical ventilation. Death rate, much higher than observed in other drug self-poisoning is a concern to be taken into account when prescribing this drug to a patient at risk of suicide attempt.

ARTICLE 2

Baclofen self-poisoning: is extrarenal epuration efficient in patient without kidney dysfunction ?

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1. Abstract

Objectives: The aim of this study was to develop a pharmacokinetic model to assess effectiveness of hemodialysis as a strategy to help patient without renal dysfunction, severely self-poisoned with baclofen.

Methods: A population was built using analytical data extracted from 26 baclofen poisoning cases reported to a French the Poison Center: 7 patients underwent hemodialysis, 18 were not hemodialysed. In each group, 1 patient suffered from renal impairment. Mechanical ventilation has been required for 20 patients without kidney dysfunction; 15 were non-hemodialysed and 5 hemodialysed. A non-parametric adaptive grip approach was used. The total data set was divided into a building data set (26 patients, 57 observations) and a validation set (2 external patients, 6 observations). Screening and selection of covariates were performed as part of the population pharmacokinetic analysis, following a classical stepwise approach.

Results: A model using three parameters plus a lag time and bioavailability (absorption phase) was necessary to determine the pharmacokinetics of baclofen in this population. Half-lives of elimination in the hemodialysis group and the no hemodialysis group were respectively 3.93 ± 2.45 h and 4.09 ± 4.02 h (p=0.256). Half-life calculated for both patients with renal dysfunction was 46 h (not hemodialysed patient) vs. 5 h (hemodialysed patient). The mean duration of intubation was not significantly different between each group (93.9 ± 56.5 h and 80 ± 44.6 h, respectively; p= 0.530)

Conclusion: Dialysis appeared to be useless in patients without kidney dysfunction with severe baclofen poisoning because of its lack of biological or clinical effectiveness.

2. Introduction

Baclofen, originally used for treatment of central spasticity, has found recently a resurgence of interest thanks to studies that has shown efficacy in the treatment of addictions as cocaine or amphetamine [2]. Olivier Ameisen, a cardiologist, described in a best seller book how he cured his alcohol addiction with daily high doses of baclofen [6]. Baclofen is indeed a derivative of γ-aminobutyric acid, is a selective agonist of the receptor GABA(B). This pharmacological profile explains the putative addictolytic and anti-craving properties, through its action on the reward circuit [10].

The number of cases of self-intoxication with baclofen in France has increased since the drug began to be prescribed to treat alcohol-dependency. When prescribed in high doses, baclofen may lead to severe poisoning. Neurological disorders (coma, seizures, respiratory depression) and cardiovascular complications (lengthening of QT interval, bradycardia, high blood pressure) have been described. To date, only a few cases of death caused by baclofen have been reported in the literature [58-60].

Baclofen intoxication requires intensive care support. Treatment is symptomatic, with supportive care and mechanical ventilation if required. In renal insufficiency patients, the half-life is enhanced significantly [25] and therefore potentially associated with a prolongation of the toxic effects of the molecule. Based on biological data collected from patients hospitalized for suicidal ingestion of baclofen, this study aimed to define the effectiveness of hemodialysis in the treatment of severely poisoned patients without renal dysfunction.

3. Materials and methods

At first, a review of the literature on oral baclofen poisoning in patients without renal dysfunction, treated by hemodialysis was made. Then, in a second time, we studied cases reported to the "Grand Ouest" Poison Control Center (PCC) (Angers University Hospital, Angers, France) retrospectively.

1. Bibliographic search strategy

Systematic review methods were used in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for conducting and reporting this systematic review [61]. A search of the PubMed electronic database was completed from inception to October 2016. The search terms were a combination of MESH terms and keywords and included "baclofen hemodialysis" or "baclofen hemofiltration" in the title, abstract, or keywords.

A manual search and screening of the bibliographies of the selected articles was performed in addition to the computerized screening. Duplicate searches were eliminated.

2. Case series

In the West French region (corresponding to the "Grand Ouest" PCC territory; 12 millions inhabitants), we identified all cases of oral baclofen poisoning in patients without renal

dysfunction, treated by hemodialysis reported to the "Grand Ouest" PCC up to 31 December 2015 from spontaneous reports. The cases between January 2012 and December 2015 were reviewed.

Data used in this study came from phone declarations from all emergency departments and intensive care units of Western France to "Grand Ouest" PCC. All cases with a known supposed dose ingested and at least one plasma dosage of baclofen collected were included.

All the pharmacokinetics profiles obtained from the 26 overdosed patients were analysed using the non-parametric adaptive grip approach implemented in a R-package (Pmetrics version 1.5.0) [62]). The total data set was divided into a building data set (26 patients, 57 observations) and a validation set (2 external patients, 6 observations). Several structural models were evaluated during the development process with and without absorption lag time (Tlag) and/or bioavailability (F). The analysis was based on a covariate-free two-compartments open model: absorption of baclofen was modelled as a first process as described in Figure 2.

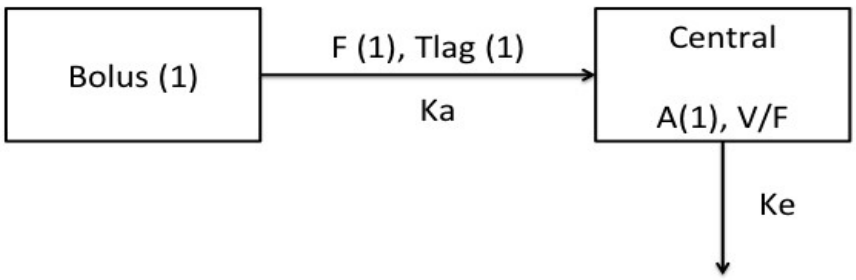

Figure 2: Schematic pharmacokinetic model structure. A 2-compartment model was constructed with a first order absorption rate constant (Ka) and an elimination rate constant (Ke). The delayed absorption process was described by Tlag and bioavailability by F. A(1) is the amount of baclofen in the central (plasmatic) compartment and V the volume of distribution of the central compartment.

Screening and selection of covariates were performed as part of the population pharmacokinetic analysis, following a classical stepwise approach. The model was parameterized in terms of F, absorption rate constant (Ka), elimination rate (Ke) and central volume of distribution (Vd). A linear error model was used to describe the analytical variability.

The performance of the model was appreciated by studying its ability to estimate the individual plasma concentration values of baclofen: The mean bias between the individual plasma concentrations calculated using the individual posthoc parameters and those observed was calculated. Goodness-of-fit plots were also generated, including observed versus predicted values at individual levels and weighted residuals versus predictions.

Baclofen half-life ($t_{1/2}$) was calculated as ln (2)/ke. Baclofen half-lives were then compared between patients with normal renal function (absence of AKIN criteria at the time of baclofen blood measurements [63]) that underwent or not renal replacement therapy. Clearances were calculated using the MDRD formula. The duration of intubation was also reported to determine the clinical effectiveness of hemodialysis between these two groups.

Between-group comparisons were performed using Wilcoxon rank sum test with continuity correction. A value of $P<0.05$ was considered statistically significant.

4. Results

Our research, without any time limitation, has selected 37 papers. Only 5 concerning oral baclofen poisoning in patients without renal dysfunction, treated by hemodialysis or

hemofiltration were finally retained: 3 cases reports with hemodialysis, one case report with continuous veno-venous hemofiltration and a retrospective review of 8 patients including 4 with CVVH [28-30,64,65]. In the first case, the elimination half-lives of baclofen before and during hemodialysis was 15.7 and 3.1 hours, respectively for an estimated dose of 420 mg ingested. Concentration of baclofen in plasma was 1.167 mg/L 12 hours after ingestion. The patient was hemodialysed 15 hours after his admission for 4 hours. His consciousness returned 9 hours after and was extubated thereafter [29]. But in the second and the third case report there was more reserve on the effectiveness of the hemodialysis. One patient ingested 3500 mg of baclofen. The serum baclofen level was estimated at 8 mg/L (H3) with $t_{1/2}$ = 7 h. She was extubated 15 days after the intoxication despite 4 sessions of hemodialysis (H40; H60; H80 and day 8) but a pharmacobezoard was suspected [64].

And in the third, the first plasma baclofen concentration measured was 2.060 mg/L after 16 hours of 3500 mg ingested. Elimination half-life was nearly 7h before 4 hemodialysis and a mean of 5.0 ± 1.8h during each 6 hours hemodialysis session. The patient woke up a day 13 and was extubated on day 15. In this case, hemodialysis did not seem to benefit to increasing baclofen elimination [65].

Concerning the case report of CVVH, the dose ingested was 340 mg and baclofen concentration 1.81 mg/L 3 hours after ingestion. The elimination half-life during hemofiltration was 4.75h and theoretical half-life in absence of hemofiltration 7.4 h. The patient became fully conscious on the third day after admission [28]. Table II summarizes the studies with renal replacement therapy in baclofen overdose to patient with a normal renal function.

Tableau II : Summary of studies with renal replacement therapy in baclofen overdose to patient with a normal renal function.

Estimated dose of baclofen (mg)	Concentration of baclofen in serum (mg/L)	Estimated half life of baclofen in absence of RRT (h)	Estimated half-life of baclofen during RRT (h)	Duration of ventilation	Type of RRT	Reference
3500	2.060 (H16)	7	5 +/- 1.8	15 days	4 hemodialysis 6h	[65]
340	1.81 (H2)	7.4	4.75	3 days	CVVH 3 days	[28]
420	1.167 (H12)	15.7	3.1	20h	1 hemodialysis 4h	[29]
3500	2.060 (H16)	7	NR	15 days	4 hemodialysis	[64]
160/200/ 600	0.719(H13)/2.304(H9)	NR	NR	1/2/4 days	CVVH 1 day	[30]

In our study, pharmacokinetic profiles were analyzed from 26 included patients. A model using three parameters plus a lag time and bioavailability to describe the absorption phase was necessary to determine the pharmacokinetics of baclofen in this population. The figure 3 illustrates the goodness of fit.

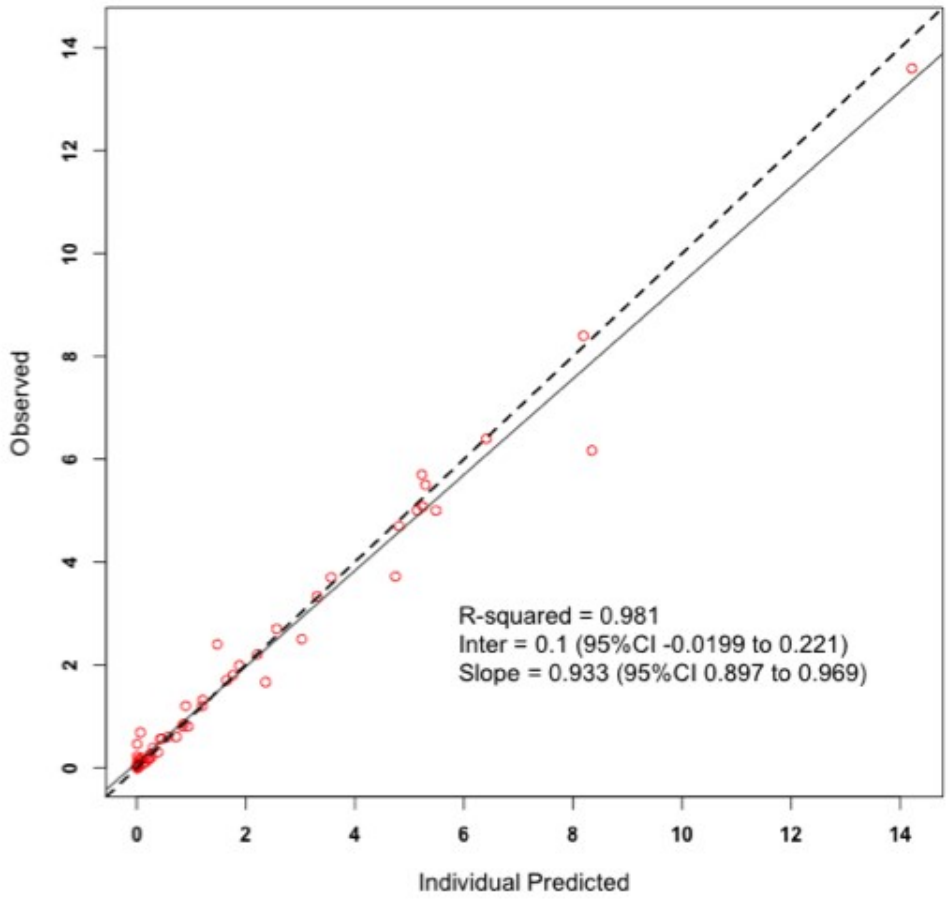

Figure 3: Goodness-of-fit plot of the pharmacokinetic model

The relative median bias between the reference and model estimated concentrations was -1.89% (25% quantile: -30.7%, 75% quantile: 17.0%). The scatter plot of observed and individual predicted concentrations showed no major bias (figure 4), and 95% of weighted residuals were within an acceptable range (-2 to 2).

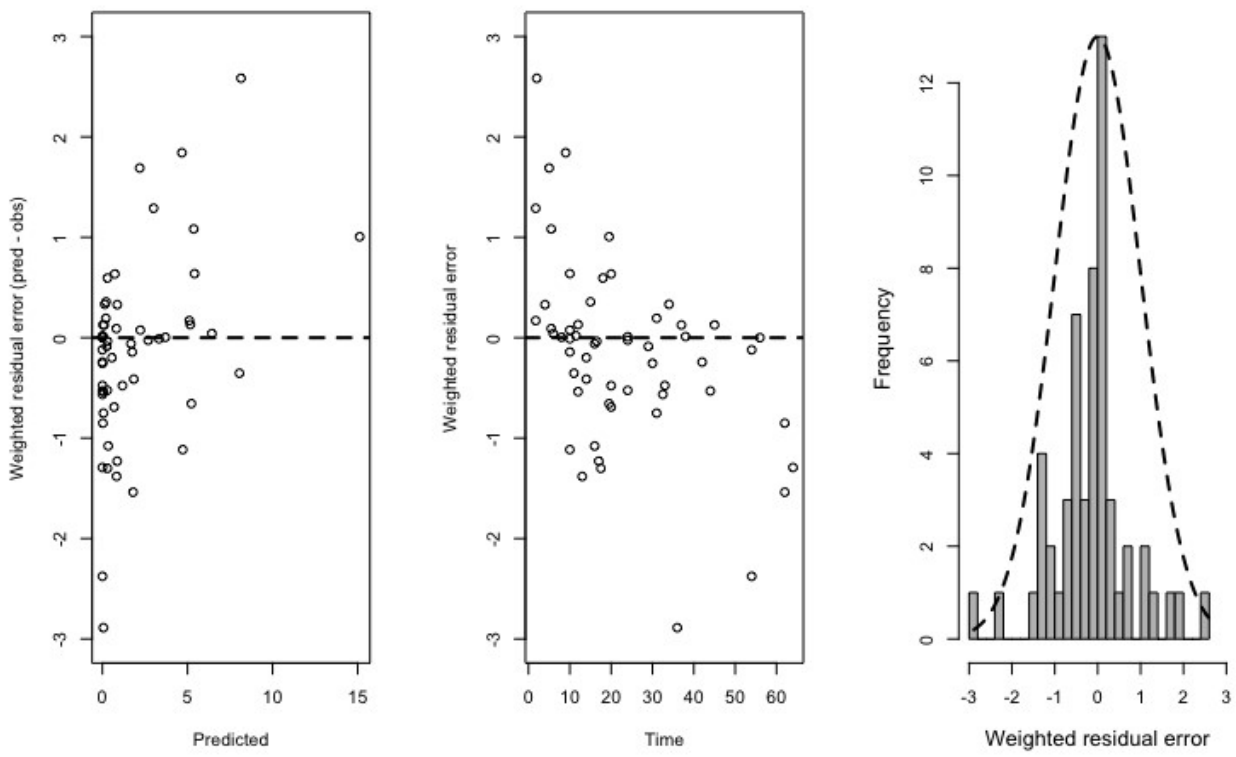

Figure 4: Weighted residuals versus predictions (left), time (middle) and histogram of residuals with a superimposed normal curve (right).

Two patients served as external validation. The goodness of fit was good (R^2=0.901) and no major bias was observed (25% quantile: -24.2%, 50% quantile: -0.4%, 75% quantile: 2.60%). Among the 26 patients, 7 underwent hemodialysis during their stay in ICU (4 male and 3 female), 19 were not hemodialysed (10 male and 9 female). In each group only 1 patient suffered from impaired renal function. The population pharmacokinetics parameters are given in table III. Estimated dose of baclofen ingested (mg) and initial baclofen levels were averaged 858.3 ± 586 mg vs. 571.6 ± 570.2 mg and 6.5 ± 3.6 mg/L vs. 2.4 ± 1.9 mg/L for the 2 groups of patients with preserved renal function, hemodialysed and non hemodialysed respectively. Clearances of creatinine were not significantly different between the 2 groups; medians were 121,5 ml/min (99 – 156) vs 112,5 ml/min (82-143) p= 0,482.

Half-lives of elimination in these patients were respectively 3.93 ± 2.45 h (ke = 0.229 h^{-1}) and 4.09 ± 4.02 h (ke = 0.365 h^{-1}). Dialysis did not appear to significantly reduce the half-life of baclofen (p = 0.526). (Table IV). Half-life calculated for both patients with Acute Kidney Injury Network (AKIN) criteria was 46 h (not hemodialysed patient, clearance of creatinine = 35ml/min) vs. 5 h (hemodialysed patient, clearance of creatinine = 38 ml/min).
A mechanical ventilation has been required for 20 patients with preserved renal function. Among them, 15 were non-hemodialysed and 5 hemodialysed. The mean duration of intubation was not significantly different between each group (93.9 ± 56.5 h and 80 ± 44.6 h, respectively; p= 0.530) (Table IV).

Tableau III: Population pharmacokinetic parameters

Parameter	**Unit of measure**	**Final model parameter estimate**
F	-	0.68 (0.5-0.9)
Ka	h^{-1}	0.92 (0.41-1.2)
Ke	h^{-1}	0.27 (0.05-0.69)
V1/F	L	16.79 (10-20)
Lag time	h	0.274 (0-4)

Tableau IV: Mean ± SD of baclofen pharmacokinetic parameters and duration of intubation for patient with and without hemodialysis

	Hemodialysed patients (n=6)	Non-hemodialysed patients (n=18)	P
Estimated dose of baclofene (mg)	858.3 ± 586	571.6 ± 570.2	0.192
Initial baclofen level (mg/L)	6.5 ± 3.6	2.4 ± 1.9	0.004
Estimated half-life (h)	3.92 ± 2.45	4.09 ± 4.02	0.526
Duration of intubation	80.0 ± 44.7 (n= 5)	93.9 ± 56.5 (n=15)	0.530

5. Discussion

Recently baclofen has represented the hope of an effective cure of addiction to alcohol, in a context where conventional treatments had modest results. But ingestion of large amount of baclofen in attempt to self-arm has been shown to be potently at risk. Several reports already insisted on the frequency and severity of baclofen-induced encephalopathy with delirium, seizures, burst suppression on the EEG and leading to mechanical ventilation, aspiration pneumonitis and eventually death [43,49-52]. Rate of intubation and mechanical ventilation has been reported from 30 to 50% in a study (unpublished data), which is a strong marker of the frequent severity intoxication. The objective of this work is to determine if dialysis is of interest in the management of patients self-poisoned with baclofen, when they have a preserved renal function.

In toxicology, the introduction of hemodialysis in the treatment of acute intoxication had the advantage to increase the elimination of toxic and shorten the duration of symptoms or severity of the poisoning. Pharmacological and physicochemical properties of baclofen make it a dialyzable molecule: hydrosolubility, small molecular weight (213.7 g/mol) and excretion

primarily unchanged by glomerular filtration. Multiple case reports of reducing elimination half-life time with renal replacement therapy (RRT) have been published, permitting a clinical improvement [26,27].

Concerning patient with a normal renal function, baclofen overdose reported half-lives up to 15.7 or 34.5 hours for a presumed ingested of 420 and 450 mg for [18,29]. Use of dialysis was relatively frequent, notably in patients without renal impairment. It reflects the debate on its usefulness in baclofen poisoning [31]. Some case reports tried to evaluate the interest of RRT in patients with preserved renal function, with a decrease of elimination half live but without find a superiority of a technique or a clinical benefit [28,30].

Charifou *et al.* described eight baclofen-poisoned patients, all managed in the intensive care unit with favourable outcomes, with four patients including three with normal renal function treated with continuous veno-venous hemofiltration (CCVH). But improve baclofen clearance and the duration of mechanical ventilation in these patients were not compared to patients with no CCVH [30]. However, faster elimination baclofen with extracorporeal therapy are already described in literature. Meulendijks *et al.* reported a decrease in half-life of 7.4 h to 4.8 h and Hsieh *et al.* a decrease in half-life of 15.7 h to 3.1 h [28,29]. On his side, Cleophax *et al.* had published a case of a severe baclofen-poisoned patient with preserved renal function treated with haemodialysis, with founding a mean haemodialysis elimination half-life close to the value found before hemodialysis [65].

For the first time, a cohort study was done to compare the effect of hemodialysis on the elimination half-life, in no renal insufficient patient. In our cohort, we did not observed decrease in half-life of elimination between patients who were undergoing hemodialysis or not. Furthermore, the calculated half-lives were similar as those observed at therapeutic doses, from 3.5h to 6.8 h [23] and thus relatively short. So, in this serie, hemodialysis was of no benefit to increasing baclofen elimination.

In the same way, the lengths of mechanical ventilation were not significantly different between patients treated or not by a renal replacement therapy. It did not seem there were toxicodynamics efficiency renal replacement. Indeed, the clinical efficacy was not demonstrated in a case report of Meulendijks *et al.* Despite biological efficacy of hemofiltration, the patient woke up only after 40 hours, while serum concentrations were undetectable past 22h [28]. Persistent neurological symptoms had also been described many times by various authors [30,39,64,66]. Indeed, we know that baclofen, moderately lipophilic, has a low diffusion in the cerebrospinal fluid. In animal studies, apparent elimination rate of nerve tissue is much slower than that of serum [67]. Furthermore, different authors observed plasma rebounds of baclofen, possibly related to a release from the CNS and lipid store, according to their assumptions [18,39,64,66].

However, a bias of this study was that both groups of patients (hemodialysis and non-hemodialysis) had very different initial baclofen levels even if they were difficult to compare because the sampling times were different. In addition, included patients achieved one or more haemodialysis at different times post-intoxication.

6. Conclusion

It seems that a renal replacement therapy is not indicated because of no biological and no clinical benefit, contrary to the risks and complications associated.

Two patient cohorts, one with hemodialysis started early and the other started late, compared to a cohort of no hemodialysed patients make it possible to refine this study. Indeed, one could observe the effectiveness of a hemodialysis if it is started early, before a concentration of baclofen in the CSF.

DISCUSSION

L'objectif de ce travail était d'évaluer, dans un contexte de prescriptions croissantes pour le traitement de l'alcoolo dépendance, l'épidémiologie, la morbidité et la mortalité du baclofène à des doses possiblement importantes et d'essayer de définir la place de l'hémodialyse dans la prise en charge de ces intoxications.

L'indication principale des prescriptions de baclofène dans les cas déclarés dans notre étude, est le traitement des troubles de dépendance à l'alcool. En effet, le nombre d'intoxications pour lesquelles le baclofène avait été prescrit dans un contexte de dépendance à l'alcool a augmenté de manière significative sur les 8 dernières années, contrairement aux intoxications dont les prescriptions étaient dans un contexte de spasticité. Cette observation s'accorde avec l'intérêt récent pour le baclofène [43,53], prescrit à des doses quotidiennes pouvant aller jusqu'à 300 mg [18,68,69].

Lors d'intoxication au baclofène, il n'est pas exceptionnel d'observer des troubles de conscience sévère. De multiples cas avec un score de Glasgow de 3 à l'admission ont été publiés [29,51,65,70,71]. Dans notre étude, la dose médiane suspectée ingérée est de 265 mg. Dans le groupe présentant une diminution sévère de la vigilance (GCS < 12), cette dose est de 400 mg, cette dose était significativement plus élevée que celle observée dans les cas moins sévères. De la même façon, l'étude de Charifou *et al.* présente 8 patients avec un score de Glasgow médian à l'admission de 5,5 (3,75–6,25) pour une dose moyenne suspectée ingérée de 250 mg [30].

Les prises importantes de baclofène induiraient impulsivité, comportements agressifs, et par conséquent pourraient augmenter le risque de passage à l'acte suicidaire [45,46]. Connaissant l'étroitesse entre la dose thérapeutique supérieure de la molécule et la dose pour laquelle on observe des effets toxiques, la sécurité des thérapies par baclofène à hautes doses doit être évaluée et discutée dans des populations à haut risque de suicide.

Dans notre étude, la sévérité clinique, évaluée par les scores SAPS 2 et SOFA, est similaire à celle rapportée dans la littérature [20,30,49,50].

En comparant avec l'étude de Baer *et al.*, étudiant 100 cas d'intoxications volontaires à différents médicaments [48], les intoxications au baclofène semblent présenter des durées de séjour et de ventilation comparables à celles d'autres types d'intoxications médicamenteuses mais la gravité accrue des intoxications au baclofène pourrait être induite par le taux important d'intubation trachéale, et ses complications associées. Comme conclu dans l'étude de Baer *et al.*, la nécessité d'une assistance ventilatoire est associée avec une atteinte du devenir à long terme. Notre étude ne permet pas de juger cet aspect. Par contre, la survenue de pneumopathies d'inhalation semble être plus fréquente. Cette complication est connue comme étant fortement associée avec une augmentation de la morbidité et de la mortalité chez les patients intoxiqués [72,73].

Le taux global de décès observé dans notre étude est de 2,6%, ce qui est plus élevé que ceux observés dans d'autres cohortes d'intoxications au baclofène [20,43,49]. De même lorsque nous comparons notre population d'intoxications volontaires au baclofène avec l'ensemble des autres types d'intoxications volontaires déclarées au CAPTV sur la même période, on observe un taux de mortalité plus important.

Malgré la nature rétrospective de l'étude, le nombre de données manquantes était faible. Mais d'autres limitations doivent être considérées. D'une part, la seule déclaration des cas les plus sévères au CAPTV amène à surestimer le taux de complications associées. D'autre part, une part significative des intoxications au baclofène qui ont été déclarées, est issue d'intoxications multiples, et l'imputabilité d'une toxicité seule au baclofène peut être discutée.

Actuellement le traitement de ces intoxications reste symptomatique avec une prise en charge réanimatoire quand cela s'avère nécessaire. Le baclofène est une molécule dialysable et l'efficacité de l'hémodialyse a été démontré dans l'épuration du toxique chez l'insuffisant rénal avec un bénéfice clinique évident [26,27]. L'efficacité de l'hémodialyse semble donc intéressante à évaluer chez le patient avec une fonction rénale normale. En effet, l'indication pourrait se poser chez ces patients avec des baclofènémies élevées dont on souhaiterait raccourcir la durée du coma et d'intubation, et donc limiter les complications associées.

Certains cas rapportés ont tenté d'évaluer l'intérêt de l'épuration extra-rénale chez les patients avec une fonction rénale conservée, avec une diminution de la demi-vie d'élimination, mais sans montrer de supériorité d'une technique sur une autre ou de bénéfice clinique [28-30].

Pour la première fois, une étude de cohorte a été réalisée pour comparer l'effet de l'hémodialyse sur la demi-vie d'élimination du baclofène, chez des patients non insuffisants rénaux. Dans notre série, l'hémodialyse ne semble pas être efficace pour accélérer l'élimination du baclofène et il ne semble pas y avoir d''efficacité toxicodynamique de l'hémodialyse, les durées de ventilation n'étant pas significativement différentes.

L'une des explications avancées serait liée à un stockage lipidique, et à un relargage plus lent du liquide céphalorachidien, responsables de rebonds plasmatiques [18,39,64,66].

CONCLUSION

Les intoxications médicamenteuses volontaires au baclofène ont considérablement augmentées au cours des dernières années, parallèlement au nombre croissant de prescriptions pour des patients dépendants à l'alcool. Ces intoxications sont caractérisées par une encéphalopathie avec une altération de la conscience, un délirium, des convulsions, nécessitant souvent une hospitalisation en service de soins intensifs et une ventilation mécanique. La dialyse ne nous semble pas être indiquée compte tenu de l'absence de bénéfice toxicocinétique ou clinique, et du fait des complications associées à la technique. Cependant, une étude de cohorte évaluant l'efficacité de l'hémodialyse débutée précocement (avant une concentration significative de baclofène au niveau du LCR), comparée à l'hémodialyse débutée tardivement ou à l'absence de son utilisation, permettrait éventuellement d'indiquer ce traitement lors des prises en charge précoces. Les baclofènémies n'étant actuellement pas obtenues en urgence, il serait nécessaire de définir les indications de la réalisation d'une hémodialyse chez un patient pris en charge dans les premières heures suivant l'ingestion des comprimés.

Le taux de mortalité, plus élevé que celui observé dans d'autres intoxications médicamenteuses volontaires est un paramètre à prendre en compte lors de la prescription de ce médicament. Le bénéfice du baclofène dans le traitement des troubles de la dépendance reste un sujet de débat, mais la communauté médicale se doit de rester alerte face aux risques inhérents à sa prescription.

Même si nous pouvons suspecter un risque surajouté de mettre en place une thérapie par du baclofène, dans une population souffrant de troubles de dépendance à l'alcool, et enclin à commettre des tentatives d'autolyse par intoxication médicamenteuse ; cette étude ne permet pas de juger le devenir à long terme dans cette population spécifique. Une étude

permettant de suivre des patients traités par baclofène dans le cadre de troubles de la dépendance sur une durée de plusieurs années, avec une prise en compte des cas d'intoxications médicamenteuses volontaires, pourrait être envisagée.

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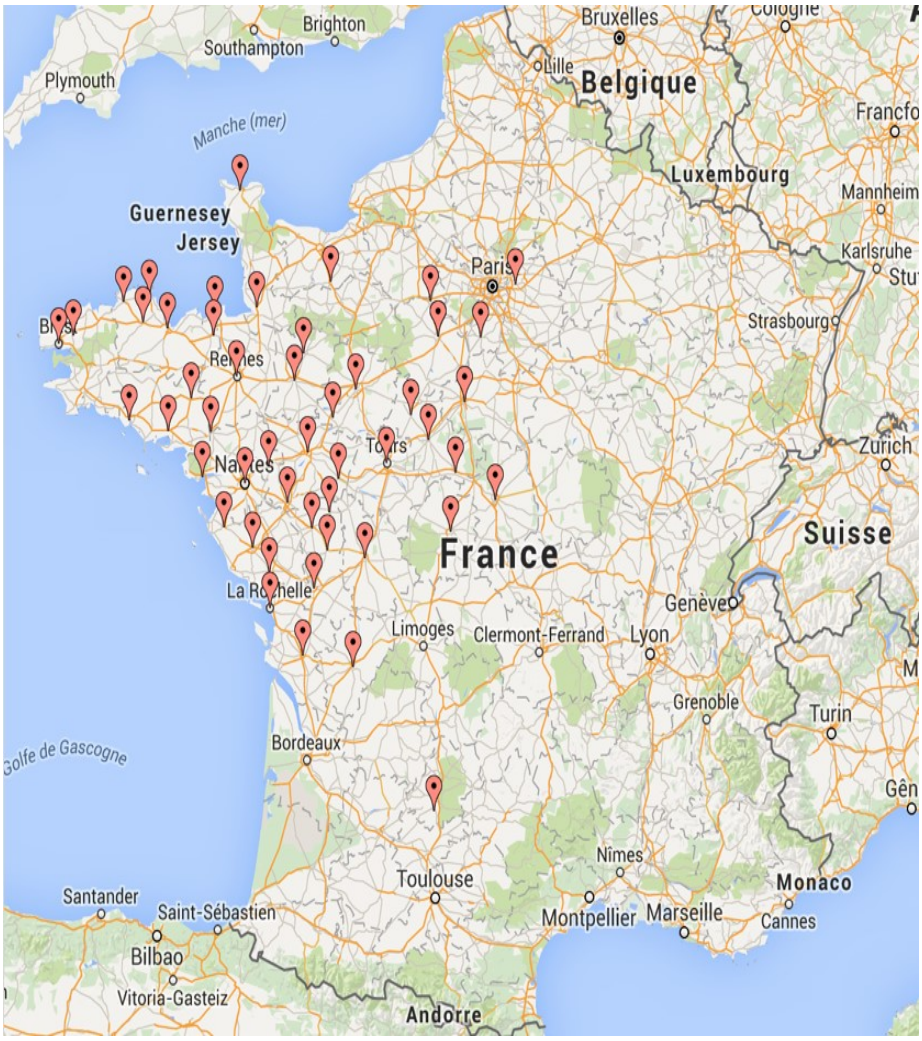
Annexe I : Location of calls, and the related map of France (using google map)

Annexe II : Others biological particularities of the population

Annexe I : Location of calls, and the related map of France (using google map)

Location of calls	GCS < 13	GCS > 12
Alençon	2	0
Ancenis	1	0
Angers	22	14
Angoulême	1	0
Call without admission	0	3
Avranches	3	0
Blois	3	1
Bourges	0	2
Bressuire	0	1
Brest	9	1
Challans	0	2
Chartres	3	1
Châteauroux	2	5
Cherbourg	2	0
Cholet	2	1
Dinan	0	2
Dreux	2	0
Etampes	1	0
Falaise	0	1
Guingamp	1	0
La Roche-sur-Yon	1	3
La Rochelle	3	0
Lagny-sur-Marne	1	0
Landerneau	0	1
Lannion	1	2
Laval	3	2
Le Bailleul	0	1
Le Mans	4	3
Lorient	0	2
Luçon	0	1
Mayenne	0	4
Nantes	7	7
Niort	1	2
Orléans	1	0
Paimpol	0	1
Parthenay	0	1
Ploermel	1	2
Poitiers	5	0
Redon	1	0
Rennes	2	1
Romorantin	0	1
Saint-Brieuc	4	2
Saint-Malo	0	2
Saint-Nazaire	5	1
Saintes	1	0
Saintonge	1	0
Saumur	1	1
Thouars	0	1
Tours	6	0
Vannes	3	0
Vendome	0	1


Brighton
Southampton
Plymouth
Manche (mer)
Guernesey
Jersey
Bruxelles
Lille
Belgique
Luxembourg
Francfo
Mannheim
Karlsruhe
Paris
Strasbourg
Zurich
Suisse
France
Genève
Lyon
Clermont-Ferrand
Limoges
Grenoble
Turin
Bordeaux
Golfe de Gascogne
Toulouse
Nimes
Monaco
Montpellier
Marseille
Cannes
Santander
Saint-Sébastien
Bilbao
Vitoria-Gasteiz
Andorre

Annexe II : Others biological particularities of the population

	Total (n=188)		**GCS ≤ 12 (n=111, 59 %)**		**GCS > 12 (n=77, 41 %)**		**p**
Blood Alcohol level, *g/dl : median(IQR)*	0 (0-1.31)		0 (0-1.22)		0 (0-1.52)		0.71
Serum Creatinine level, *µmol/l : median (IQR)*	61.5 (54-76)		61 (50-76)		65 (59-73)		0.93
Lactatemia, *mmol/l: median (IQR)*	NR		1.61 (1-2.8)		NR		
Serum CPK level, *UI/l: median (IQR)*	NR		326 (100.5-2521)		NR		
Dosage of Serum Baclofen Level, n (%)	35 (18.4%)		31 (27.4%)		4 (5.2%)		< 0.0001
Serum Baclofen level, *mg/l: median (min-max)*	2.7 (0-14.82)		3.24 (0.05-14.82)		0.32 (0-1.664)		0.00012

BRUNET Marion et LEGER Maxime

Intoxications volontaires au baclofène : présentation clinique et stratégie thérapeutique. Etude multicentrique rétrospective au Centre antipoison Grand Ouest

RÉSUMÉ

Introduction : Le manque d'un traitement efficace dans le maintien de l'abstinence éthylique a forcé les médecins à s'intéresser au baclofène. Derrière son efficacité, la sécurité de ce traitement est un enjeu, spécialement dans les cas d'intoxications. Nous avons étudié de manière rétrospective la morbidité et la mortalité associées aux intoxications au baclofène. Un intérêt particulier a été apporté aux sujets sans dysfonction rénale traités par épuration rénale.

Matériels & méthodes : Un cas a été déterminé comme une exposition volontaire au baclofène, avec ou sans symptômes, entre janvier 2008 et Décembre 2015. Cette étude était basée sur des données collectées au centre antipoison (CAP) d'Angers. Le taux de mortalité des intoxications au baclofène a été comparé avec les 31859 cas d'intoxications médicamenteuses volontaires (hors baclofène) déclarées au CAP d'Angers sur la même période. Les temps de demi-vies d'élimination ont été déterminés à l'aide d'un modèle pharmacocinétique.

Résultats : 190 cas d'intoxications ont été reportés, incluant deux décès à la prise en charge. 111 patients (59%) avaient un GCS ≤ 12 à l'admission et 77 avaient un GCS > 12 (41%). 80 patients nécessitaient de la ventilation mécanique (42,6%). Trois patients sont décédés en intra-hospitalier (mortalité hospitalière 1,6%, totale 2,6%). Les autres cas d'intoxications présentaient un taux plus faible d'intubation (6%) et de mortalité (0,1%). La demi-vie d'élimination spontanée déterminée pour 18 patients sans atteinte de la fonction rénale était de 3,93 h. Pour les six patients qui ont été traités avec de la dialyse, pour des raisons toxiques, mais sans atteinte rénale évidente, la demi-vie était de 4,08 h.

Conclusion : Le baclofène, prescrit à haute dose, peut entrainer des intoxications sévères, nécessitant fréquemment une intubation orotrachéale, et sont associés à un risque augmenté de décès. Devant l'absence d'efficacité sur l'élimination du toxique et sans bénéfice clinique démontré, l'épuration extra-rénale ne semble pas avoir un intérêt dans la prise en charge de ces intoxications.

Mots-clés : Baclofène, intoxication, revue, mortalité, temps de demi-vie, épuration extra-rénale

Baclofen voluntary poisoning: clinical presentation and treatment strategy. Retrospective multicentric study in "Grand Ouest" Poison Control Center

ABSTRACT

Introduction: The lack of an effective treatment for the maintenance of abstinence from alcohol has led physicians to take in interest in baclofen. Beyond efficacy, safety of baclofen is a concern, especially in case of drug overdose. We set up a retrospective study to describe morbidity and mortality associated with baclofen overdose.

Materials & methods: A case was defined as exposure to baclofen in self-harm attempt with or without symptoms between January 2008 and December 2015. This study was based on data collected by the Poison Control Center (PCC) of Angers University Hospital. The mortality rate of baclofen poisoning cases was compared to the 31859 non-baclofen voluntary drug-poisoning cases declared to the PCC of Angers University Hospital over the same period. Baclofen elimination half-lives were determined using a pharmacokinetic model.

Results: 190 cases of voluntary intoxications were reported, including two deaths diagnosed at first medical assessment. 111 patients (59%) had GCS ≤ 12 at admission and 77 had GCS > 12 (41%). Eighty patients required mechanical ventilation (42.6%). Three patients died in the hospital (hospital mortality rate 1.6%, total mortality rate 2.6%). Non-baclofen cases had lower rate of endotracheal intubation (6%) and mortality rate (0.1%). Spontaneous baclofen elimination half-life was calculated in 18 patients without renal dysfunction and was 3.93 h [min-max=1.89-8.35 h]. In the six patients who underwent dialysis for toxicological reason without evidence of renal failure, baclofen half-life was 4.09 h [min-max=0.78-14.2h].

Conclusion: Baclofen, prescribed in high doses, may lead to severe intoxications: self-poisonings frequently require endotracheal intubation and are associated with an increased risk of death. In the absence of efficiency on the elimination of toxic and no clinical benefit demonstrated, renal replacement does not seem to have an interest in the management of these poisonings.

Keywords: Baclofen, poisoning, review, mortality, elimination half-live, renal replacement therapy

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